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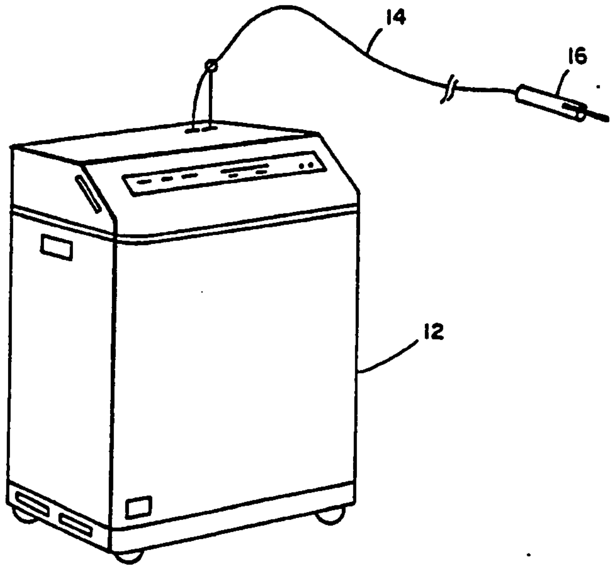

(57) Abstract

A cutaneous pigmented lesion is treated by irradiation with laser light of between 345 and 600 nm and preferably about 500 nm wavelength. The fluence is between 1 and 10 J/cm^2 and preferably between 2 and 4 J/cm^2. The pulse duration is less than 1 µsec and preferably less than 500 nsec. A 3 mm diameter spot is illuminated.

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APPARATUS AND METHOD OF TREATING PIGMENTED LESIONS USING PULSED IRRADIATION

Background of the Invention

Superficial benign cutaneous pigmented lesions such as lentigines, cafe' au lait and nevus spilus are commonly seen in dermatologic practice. A myriad of therapeutic modalities including liquid nitrogen, electrocautery and depigmenting chemicals have been used to remove them. Although widely used, none have succeeded in destroying the abnormal pigmented cells alone without damaging adjacent structures and producing adverse effects like hypopigmentation.

Over the last two decades, there have been several reports describing the removal of these pigmented lesions by a variety of lasers such as the excimer (351 nm), argon (488,514 nm), ruby (694 nm), Nd:YAG (1060 nm), and CO_2 (10,600 nm) lasers. However, there has generally been damage to both pigmented and nonpigmented cells. Pigmented lesions treated by laser have included lentigines, nevi, melanomas, oral hypermelanosis of Peutz-Jeghers syndrome, the nevus of Ota, and a lentigo maligna. The pigment depth of these laser-treated lesions has also varied significantly, from superficial lentigines in the epidermis to lesions lying deep in the reticular dermis like the nevus of Ota.

Previous studies reporting "successful" removal of pigmented lesions have relied on clinical assessment rather than on histology and have used widely divergent wavelengths, pulse durations, energy densities and spotsizes. There has been no effort to define laser parameters necessary for optimal removal of pigmented lesions.

Melanin, an endogenous cutaneous pigment which is most concentrated in the basal layer of the epidermis, has an absorption spectrum that is highest in the ultraviolet range and gradually diminishes toward the infrared. Melanosomes, which are melanocyte-specific organelles, densely packed with melanin, are predominantly found within melanocytes. They vary in size according to their genetic origin; black skin typically containing larger melanosomes than lightly pigmented, white skin. Based on melanosome size, the calculated thermal relaxation time for these organelles is around 10 nsec. On the other hand, melanocytes are approximately 7 μm in diameter, with thermal relaxation times around 1 μsec. Thermal relaxation time in both instances is defined as the time taken for a structure to cool to 50% of its peak temperature immediately after laser exposure.

Recent studies have applied the technique of selective photothermolysis to specifically destroy melanosomes using the XeF pulsed excimer _in vitro_ and the Q-switched ruby lasers _in vivo_. Histologically, both these studies demonstrated melanosomal injury that was associated with disruption of melanocytes as well as melanin-containing basal keratinocytes. In addition, there was also evidence of follicular damage after exposure of pigmented guinea pig skin to the Q-switched ruby laser.

Disclosure of the Invention

In accordance with the present invention, specific laser parameters are established to obtain effective treatment of cutaneous pigmented lesions, particularly epidermal lesions, while minimizing damage to normal pigmented cells. Specifically, effective treatment with minimal damage has been obtained with a laser having a wavelength of about 500 nm, a pulse duration of about 500 nsec, and fluence (energy density) of about 3 J/cm^2. The preferred spotsize is 3 mm.

To minimize damage, wavelength should be less than 600 nm. Due to known problems of mutagenesis, the wavelength should not be less than 345 nm.

The fluence may range from 1.0 to 10 J/cm^2 through the full range of wavelengths, but is preferably within the range of 2 to 4 J/cm^2 for 504 nm light. Pulse durations approaching 1 μsec may be used but at 1 μsec recurrence is expected. Shorter pulse durations should minimize damage to normal tissue. Shorter pulses increase the laser intensity for a given fluence, and durations of less than 100 nsec with 2 J/cm^2 may stress the optical components of the system, particularly a fiber-optic delivery mechanism.

To avoid pigmentary incontinence of the epidermal pigment resulting from laser irradiation and to get better access to dermal pigment to effectively treat deeper pigmented lesions, a proposed method of treating dermal lesions is to create a window in the epidermis using the above defined laser parameters and then treating the deeper cells with a laser having parameters specific to those cells. It is expected that longer wavelengths will be optimal to achieve such depths of penetration.

Brief Description of the Drawings

Fig. 1 illustrates a laser having a fiber and handpiece delivery system for practicing the invention.

Fig. 2 is an enlarged perspective view of the handpiece.

Description of Preferred Embodiments

A wide range of experimental treatments have been performed on the normally pigmented skin of miniature black pigs and those have been followed by extensive clinical studies. A first set of experiments was performed to identify shorter wavelengths in the green portion of the spectrum for the minimization of dermal damage, particularly pigmentary incontinence, as well as regeneration of normal pigment cells. A second set of experiments using the optimum laser wavelength of 504 nm has identified shorter pulse durations as preferred for minimizing damage. Finally, clinical studies of human patients have demonstrated that laser light of the shorter wavelengths and shorter pulse durations is most effective in treating the pigmented lesions where the fluence is about 3 J/cm^2. Limited human pigmented lesion studies have demonstrated lack of effectiveness at 694 nm and 750 nm.

In the experiments, a Model SLL500-M flashlamp-pumped tunable dye laser system 12 supplied by Candela Laser Corporation has been used. The light is delivered through a 1 mm diameter optical fiber cable 14 to a handpiece 16 to illuminate a spot of 1 to 3 mm with a single pulse. The handpiece, illustrated in Fig. 2, is model number 7040-00-6231 supplied by Candela Laser Corporation. Two lenses in the handpiece image the distal end of the fiber to a larger spot adjacent to the end of a positioning extension 18. By selection of the lenses, the spotsize can be varied. By movement of the handpiece and irradiation of adjacent spots, a test site of about 0.5-1.0 cm x 0.5-1.0 cm is irradiated at a selected dose.

In the first set of experiments on normal black pig skin, the tunable dye laser was tuned to 504, 590, 694, 720 and 750 nm using a variety of dye mixtures. The laser had a pulse duration of 500 nsec. Energy densities ranging from .25 to 3.0 J/cm^2 at 0.25 J/cm^2 increments, and at 4.0, 5.0, 6.0 and 7.0 J/cm^2 were delivered to pigmented skin at a spotsize of 3 mm diameter. The skin was irradiated at each energy density for each of the five wavelengths tested. Skin biopsies were taken at each energy density from each of the five wavelengths immediately and at 4, 16, 23 and 33 days after laser exposure. These experiments were published by Sherwood et al., "Effect of wavelength on cutaneous pigment using pulsed irradiation," The Journal of Investigative Dermatology, Vol. 92, No. 5, May 1989.

Exposure of skin to energy densities of at least 5 J/cm^2 for 590 and 694 nm and 4.0 J/cm^2 for 720 and 750 nm resulted in sub-epidermal clefts accompanied by epidermal necrosis. No sub-epidermal clefts or epidermal necrosis were observed after exposure of skin to 504 nm irradiation, not even at the highest energy density of 7.0 J/cm^2. In addition to epidermal injury, dermal damage consisting of collagen bundle separation accompanied by changes in the tinctorial quality of the bundles were observed in biopsies taken from the skin exposed to 7.0 J/cm^2 at the four wavelengths other than 504 nm. The extent of dermal injury appeared dependent on the wavelength; the most severe occurring at 750 nm.

From biopsies, pigmentary incontinence (pigment dropping to the dermal layer) was evident. Its severity increased with increased energy density and wavelength.

Although pigment was destroyed using all wavelengths, repigmentation occurred more rapidly for the 504 nm irradiation. For the 504 nm irradiation, repigmentation was complete by the thirty-third day after exposure. Repigmentation followed sequentially by order of wavelength, with the 750 nm irradiated skin taking up to six weeks for its pigment to return to normal.

In the second set of experiments, miniature black pig skin was again irradiated. Using a 504 nm laser and 3 mm diameter spotsize, the effect of pulse durations of 100, 150, 250 and 500 nsec at fluences from 1.5 to 4.0 J/cm^2, at 0.5 J/cm^2 increments, were examined. Biopsies were taken immediately and at 7, 14 and 28 days after irradiation and were processed for light microscopy. The most severe damage was observed in skin exposed to pulse durations of 250 and 500 nsec. Epidermal necrosis, dermal-epidermal separation and pigmentary incontinence were not only more severe, but also occurred at significantly lower fluences than was evident in skin exposed to 100 and 150 nsec pulse durations. Although the normal cells repigment, the unsightly damage remains.

In the final clinical studies with human patients, superficial benign cutaneous pigmented lesions had been treated by using the pulse irradiation. Fifty-two patients have been treated variously for the following: lentigines, solar keratoses/'lentignes', cafe' au lait, seborrheic keratoses, hyperpigmentation associated with morphoea, nevus spilus.

Generally, the lesions have been exposed to 504 nm laser irradiation. Pulse durations of 250 nsec, 500 nsec and 1 μsec have been used with fluence ranging from 1.5 to 3.5 J/cm^2 for each pulse duration. A 3 mm diameter spotsize was used with the 500 nsec and 1 μsec pulse durations. Because of limits in energy available from the particular laser used, a 2 mm diameter spotsize was used with 250 nsec pulse durations. A 1 mm diameter spotsize was used in limited tests of 6 to 8 J/cm^2, but excessive dermal damage was noted. This is consistent with findings presented in Tan et al., "Spotsize effects on guinea pig skin following pulsed irradiation," The Journal of Investigative Dermatology, Vol. 90, No. 6, June 1988. At all pulse durations, incomplete lightening was found at 2 J/cm^2 and 2.5 /cm^2. The 3.0 J/cm^2 was found to be the most effective dose. The 3.5 J/cm^2 was only used in a limited number of tests where insufficient response was obtained at 3.0 J/cm^2 and was effective. With the 1 μsec pulse duration, the lesions cleared but recurred. At 500 nsec, nonrecurring clearance was obtained. At 250 nsec, clearance was also obtained, and we are awaiting final results. Clinical observations indicate minimal dermal damage without noticeable pigmentary incontinence.

With limited tests at 504 nm and 4 J/cm^2, some permanent loss of normal pigment and undesirable surface changes were noted. However, with appropriate selection of other parameters, higher fluences may be feasible.

Limited tests of a 694 nm Q-switched ruby laser having a pulse duration of 20 nsec and fluence of 5 J/cm^2 proved ineffective in removing the lesions. Similarly, a Q-switched alexandrite laser of 760 nm, 100 nsec and 3 J/cm^2 was ineffective in treating the lesion with a 2mm spotsize.

Limited tests at 577 nm, 360 nsec resulted in clearance of the lesion but with recurrence. However, lesions are expected to be effectively treated with that wavelength at shorter pulse durations. To minimize adverse effects, particularly due to pigmentary incontinence, wavelengths of about 600 nm or less are judged best from the first set of experiments.

Although 504 nm is the shortest wavelength tested, it is the most effective, and it is expected that shorter wavelengths within the melanin absorption spectrum will provide desirable results. Due to concerns for mutagenesis, wavelengths of less than 345 nm should not be used. It is postulated that the shorter wavelengths are most effective with least damage because they are absorbed by blood in the dermis and thus create thermal effects which minimize pigmentary incontinence.

It is expected that the acceptable fluence range is a function of wavelengths. At 504 nm, some effect on melanin is noted at 2 J/cm^2, and damage is seen above 4 J/cm^2. The depth of penetration in caucasian skin, which is inversely related to absorption, for 350 nm, 500 nm, 600 nm and 700 nm is about 60 μ, 230 μ, 550 μ and 750 μ, respectively. Thus, expected ranges of effect without damage, based on the 2 to 4 J/cm^2 range at 504 nm, is about 0.5 to 1.0 J/cm^2 for 345 nm, and 5 to 10 J/cm^2 for 600 nm. In general, it is expected that fluences of 1 to 10 J/cm^2 will be used for wavelengths of 345 nm to 600 nm.

The above described tests indicate that pulse durations of even less than 500 nsec are desirable. Lasers capable of generating pulse durations less than 100 nsec and wavelengths in the preferred region are Q-switched, frequency doubled Neodynium lasers which include Nd:YAG, Nd:Glass and Nd:YLF. These lasers generate output wavelength in the range 527 to 532 nm and pulse durations in the range of 5 to 50 nsec. At pulse durations of less than 100 nsec, delivery systems such as articulated arms or liquid-filled light guides may be required, and general stress on system optics may be excessive. However, with shorter pulse durations, it is expected that lesser fluences may be used.

On the other hand, treatment of pigmentary lesions in the dermis are of interest, and longer wavelengths are expected to be more effective due to greater depths of penetration. A problem encountered with longer wavelengths is that of pigmentary incontinence where pigment from the epidermis is driven to the lower dermis. One means of treating the deeper lesions with longer wavelengths without pigmentary incontinence is to remove the pigment in the epidermis using the shorter wavelengths and subsequently treat the lower regions with longer wavelengths. Thus, the shorter wavelengths remove the pigment from the epidermis to create a window through which the light can pass into the dermis. Without pigment in the epidermis, illumination using the longer wavelengths cannot cause the pigmentary incontinence.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

CLAIMS

1. Apparatus for treating cutaneous pigmented lesions comprising:

a laser which produces a beam of 345 to 600 nm wavelength, 1 to 10 J/cm^2 fluence, and less than 1 µsec pulse duration; and

a delivery system for delivering the laser beam to illuminate the pigmented lesion.

2. Apparatus as claimed in Claim 1 wherein the laser produces a beam of about 500 nm wavelength, 2 to 4 J/cm^2 fluence, and 500 nsec or less pulse duration.

3. Apparatus as claimed in Claim 1 or 2 wherein the laser is a flashlamp excited dye laser.

4. Apparatus as claimed in Claim 1 or 2 wherein the laser is a Q-switched, frequency doubled Neodymium laser.

5. Apparatus as claimed in Claim 1, 2, 3 or 4 wherein the delivery system illuminates a region of about 3 mm diameter.

6. Apparatus as claimed in Claim 1, 2, 3 or 4 wherein the delivery system illumninates a region of about 2 mm diameter.

7. Apparatus as claimed in Claim 1, 2, 3, 4, 5 or 6 wherein the pulse duration is about 100 nsec.

8. Apparatus as claimed in Claim 1, 2, 3, 4, 5 or 6 wherein the fluence is about 3 J/cm.

9. A method of treating epidermal pigmented lesions comprising irradiating the epidermis with laser radiation of wavelength between 345 and 600 nm, fluence of 1 to 10 J/cm^2 and pulse duration of less than 1 μsec.

10. A method as claimed in Claim 9 wherein the fluence is between 2 and 4 J/cm^2.

11. A method as claimed in Claim 9 and 10 wherein the fluence is about 3 J/cm^2.

12. A method as claimed in Claim 9, 10 or 11 wherein the pulse duration is about 500 nsec or less.

13. A method as claimed in Claim 9, 10, 11 or 12 wherein the pulse duration is about 100 nsec.

14. A method as claimed in Claim 9, 10, 11, 12 or 13 wherein the laser illuminates a spot of about 3 mm diameter.

15. A method as claimed in Claim 8, 10, 11, 12 or 13 wherein the laser illuminates a spot of about 2 mm diameter.

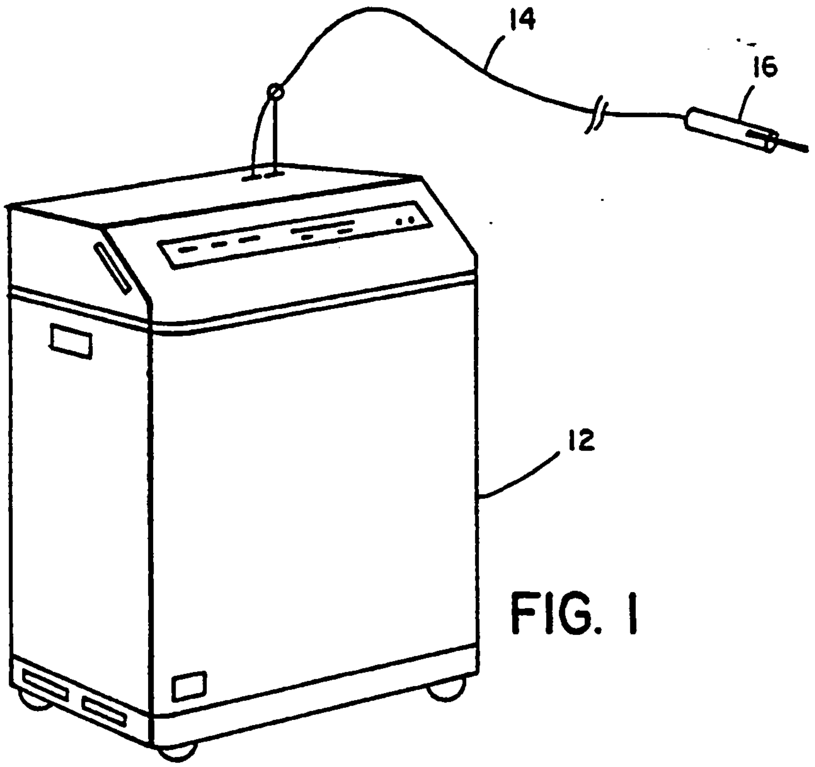

FIG. 1

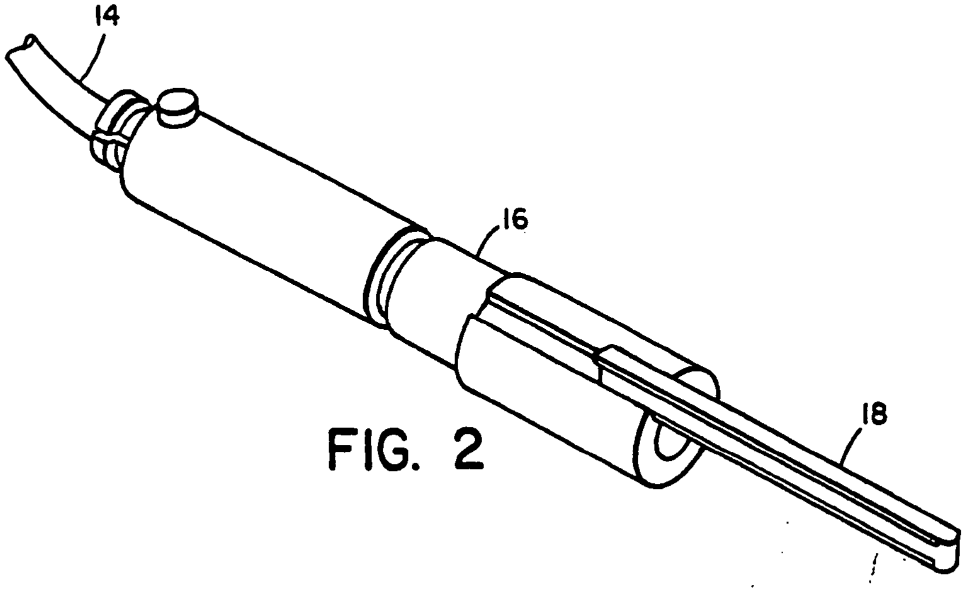

FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/01715

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC^5: A 61 N 5/06

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC^5	A 61 N

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0172490 (ITZKAN) 26 February 1986 see page 5, lines 6-22 ---	1-8
X	Lasers in Surgery and Medicine, volume 1, 1981, R.R. Anderson et al.: "Microvasculature can be selectively damaged using dye lasers: A basic theory and experimental evidence in human skin", pages 263-276	1-8

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 9th July 1991	Date of Mailing of this International Search Report 19.08.91
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer miss T. MORTENSEN

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers 9 - 15 because they relate to subject matter not required to be searched by this Authority, namely:

Pls. see Rule 39.1 (iv) - PCT

Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the international application
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9101715
SA 45796

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 06/08/91
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0172490	26-02-86	JP-A- 61058673	25-03-86
		US-A- 4733660	29-03-88

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82